Scientific Abstract

Chronic, neutrophil-dominated, lung inflammation is important in the pathogenesis of CF lung disease. Normal host defenses, particularly the antiprotease α-1 antitrypsin (AAT), are overwhelmed by the inflammatory burden and cannot protect the lung from the injurious effects caused by neutrophils. Augmentation therapy with AAT has been proposed to restore the normal protease/antiprotease balance. However, it has been difficult to prove clinical efficacy of antiprotease therapy in CF patients, mainly because of a limited supply of purified antiprotease protein.

We believe that AAT gene therapy (as opposed to AAT protein therapy) is a better strategy for restoring antiprotease defense mechanisms because expression of the AAT gene in lung cells may, in addition to neutralizing neutrophil elastase, provide antiproteolytic and antiinflammatory effects. We are developing the nasal lavage model as a means of studying the inflammatory response of respiratory epithelium *in vivo*. In this proposal, we plan to define the inflammatory state of the nasal mucosa more thoroughly in CF patients, paying particular attention to markers of the protease/antiprotease imbalance, then test two hypotheses. The first hypothesis is that the AAT gene can be effectively delivered to the nasal mucosa in CF subjects using plasmid/cationic liposome complexes and the second is that expression of the AAT gene locally in the respiratory tract will suppress the inflammatory response. Specifically we propose:

1. To characterize the inflammatory state of the nasal mucosa in patients with CF compared to healthy controls by: a) measuring in nasal lavage fluid the concentrations of inflammation-related cytokines, AAT protein, free elastase, and collagen degradation products; and b) determining in nasal mucosal scrapings the numbers of inflammatory cells present and which inflammation-related cytokine genes are expressed.

2. To determine whether the AAT gene can be delivered to the nasal mucosa of patients with CF using cationic liposomes and to define the magnitude and time course of transgene expression.

3. To determine whether transfer of the AAT gene to the nasal mucosa of patients with CF decreases inflammation and production of proinflammatory cytokines.